IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	AUDONNET et al.
Serial No.	:	09/766,442
Filing Date	:	January 19, 2001
For	:	IMPROVED DNA VACCINES FOR FARM ANIMALS, IN PARTICULAR BOVINES AND PORCINES
Examiner	:	J. Eric Angell
Art Unit	:	1635

745 Fifth Avenue, New York, NY
10151

EXPEDITED PROCEDURE
RESPONSE AFTER FINAL ACTION
UNDER 37 C.F.R. 1.116

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DECLARATION UNDER 37 C.F.R. 1.132

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Commissioner for Patents
P.O. Box 1450
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Dear Sir:

I, Dr. Jean-Christophe Audonnet, declare and state that:

1. I make this declaration in connection with U.S. application Serial No. 09/766,442. I am a co-inventor of this application and am familiar with its prosecution history, particularly as it pertains to the rejection under 35 U.S.C. §103(a) of claims 1, 4, 5, 16-19 and 21-36 as allegedly being unpatentable over Taylor *et al.* in view of Harris *et al.* and in further view of Bonnem *et al.* and Baker *et al.* Moreover, I am familiar with the final Office Action mailed on August 26, 2003.

2. I am a citizen of France. As indicated on my attached *Curriculum vitiae*, I received a veterinary degree from Ecole Nationale Vétérinaire d'Alfort in 1980, a master's degree in molecular biology and genetics from University Montpellier in 1984, and a doctorate in molecular biology from Lyon University in 1989. I have also received a Certificate of Compared and Animal Immunology, a Certificate of Immunology and a degree in general virology. I have been employed by Merial, the assignee of this application, since September, 1997, and have served as Director of Molecular Biology and Immunology since May, 2001. From June, 1993 to September, 1997, I was employed as Head of the Molecular Biology and Genetic Recombination Units by Merial's predecessor company, Rhône Mérieux Lyon. In view of my education and experience, I consider myself to be an expert in the field to which this application pertains.

3. The August 26, 2003 Office Action alleges that the combination of Taylor *et al.*, Harris *et al.*, Bonnem *et al.* and Baker *et al.* renders the instant invention obvious. The Office Action argues that Taylor *et al.* teaches a DNA vaccine, and that Harris *et al.* teaches a therapeutic molecule complexed to DMRIE and DOPE, for enhanced intracellular delivery. Bonnem *et al.* and Baker *et al.* relate to GM-CSF, which is only applicable to claim 19, and will be discussed separately. It should initially be noted that Taylor *et al.* does **not** teach a DNA vaccine, as alleged in the Office Action. Rather, Taylor *et al.* used a recombinant vaccinia virus to express BRSV antigens. It should be appreciated that a virus modified with cDNA to express a particular antigen is distinct from a cDNA plasmid that encodes the antigen. Taylor *et al.* relates to the former, while the instant application is concerned with the latter.

4. It should further be noted that the pending claims relate to the administration of a combination vaccine, comprising (a) a complex of a cationic lipid and a plasmid expressing an immunogen of a bovine or porcine pathogen and (b) a second vaccine, immunogenic, or immunological composition that is an inactivated, attenuated live, subunit or recombinant vaccine, immunogenic, or immunological composition. Taylor *et al.* does not teach or suggest the use of even one DNA plasmid vaccine, let alone a combination of two vaccines, immunogenics or immunological compositions. Rather, Taylor *et al.* vaccinated calves with a vector expressing only one antigen. Harris *et al.* does not remedy this deficiency. While Harris *et al.* does suggest, in the paragraph bridging columns 7 and 8, that multiple cationic amphiphiles and active molecules may be used, this suggestion relates only to delivery of unspecified

biologically active molecules, and does not address the special problems associated with eliciting an immune response, namely efficacy interference.

5. Efficacy interference occurs in a combination composition, and is a failure of an antigen to maintain or achieve efficacy, when administered in combination with another **antigen** (**not** an adjuvant, such as GM-CSF). Interference with respect to the first antigen's ability to stimulate an immunological, antigenic, antibody, or protective response in a host to which it is administered, is due to the presence of the other antigen(s). An example of an instance in which efficacy interference occurs was given in the Amendment and Response that was filed on June 10, 2003. When rabies antigens are given, particularly to dogs, in a combination with other antigens, interference occurs with the stimulation of an immunological or protective response by the other antigens in the composition, such that the efficacy with respect to the rabies antigen is reduced or abrogated. Taylor *et al.* did not and could not have addressed the issue of efficacy interference because it does not teach the administration of a composition having more than one antigen. Harris *et al.* did not and could not have addressed the issue of efficacy interference because it is directed to gene therapy, not immunological protection. Since the combination of Taylor *et al.* and Harris *et al.* do not teach, suggest or render obvious the instant invention, neither can their combination with Bonnem *et al.* and Baker *et al.*, which deal exclusively with GM-CSF, a molecule that is only even of issue in claim 19.

6. Therefore, one skilled in the art, appreciating the problem of efficacy interference, would not have reasonably expected success in combining the vaccine, immunogenic or immunological compositions of parts (a) and (b) of claim 1 to obtain an immunological response. Success, in this instance, was demonstrated by the data presented in the current application. Examples 16 and 17, show that a mixture of DNA plasmid vaccines against BHV-1 and PRV, respectively, were efficacious. These Examples directly demonstrate that the method of claim 1, namely, producing an immunological response in vaccinated animals using at least two DNA vaccines or immunogenic or immunological compositions against a bovine or porcine pathogen, wherein at least one of the vaccines or compositions also contains a cationic lipid, is effective. This is a surprising result, given the known problem of efficacy interference in the art.

7. In view of the foregoing, it is my opinion, as one of skill in the art, that there could have been no reasonable expectation of success for achieving a protective immunogenic response using a combination of (a) a DNA plasmid vaccine plus a cationic lipid and (b) a

second inactivated, attenuated live, subunit or recombinant vaccine or immunogenic or immunological composition, based on the cited art. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are requested.

8. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: January 14th, 2004

Jean-Christophe Audonnet